

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 October 2000 (03.10.00)	
International application No. PCT/GB00/00244	Applicant's or agent's file reference P020831WO
International filing date (day/month/year) 28 January 2000 (28.01.00)	Priority date (day/month/year) 29 January 1999 (29.01.99)
Applicant ADAMS, David, Reginald et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
25 August 2000 (25.08.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Zakaria EL KHODARY Telephone No.: (41-22) 338.83.38
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14



Applicant's or agent's file reference P020831WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/00244	International filing date (day/month/year) 28/01/2000	Priority date (day/month/year) 29/01/1999	
International Patent Classification (IPC) or national classification and IPC C07D487/04			
Applicant CEREBRUS PHARMACEUTICALS LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 25/08/2000	Date of completion of this report 29.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Friebel, F Telephone No. +49 89 2399 8552 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00244

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-53 as originally filed

Claims, No.:

1-34 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00244

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 28-30.

because:

- ☒ the said international application, or the said claims Nos. 28-30 - IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-34
	No: Claims
Inventive step (IS)	Yes: Claims 1-34
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-27, 31-34

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/00244

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

point III:

Claims 28-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

point V:

The present application claims substituted pyrazinoindoles which are selective 5-HT₂ receptor ligands and may be used inter alia as anti-obesity agents.

Closest prior art is on the one hand side the scientific paper cited on page 3 of the application **Med.Chem.Res.** 3, 240 (1993) (D1) and on the other side the document **EP-A-572863 (D2)** cited in the Intern.Search Rep.

D1 discloses 1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole and 3-ethyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole and their 5-HT_{1a} and 5HT₂ binding affinity. The compounds claimed differ from these prior art derivatives in that the aromatic portion is at least mono-substituted; see the proviso at the end of Claim 1.

D2 refers to 1,2,3,4-tetrahydropyrazino[1,2-a]-indoles which are serotonin antagonists and show also a 5HT₂ receptor affinity. The structural difference resides in this case in the double bond at C-10 which is saturated in the instant case.

Due to these structural differences novelty is acknowledged; Art.33(2) PCT.

As concerns inventive step the Applicant in response to the Written Opinion - convincingly argued that in the light of D1 it would not have been obvious to saturate the C-10 double bond of the prior art compounds of D2 since a comparison of the Ki (5HT₂) data given in D1 for the compounds 5 and 6 (and also / and 8) shows indeed that the respective saturated compound has a higher Ki and is therefore less strongly binding than the unsaturated compound; the inventive step requirement is therefore deemed to be met; Art.33(3) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00244

For the assessment of the present claims 28-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

point VII:

A brief reference to the document D2 is missing from the description; Rule 5.1(a)(ii) PCT.

point VIII:

Claim 1 does not meet the clarity requirement for the following reasons:

The term 'lower alkyl' (def. of R1 to R3) should be specified in the light of the description page 4 , lines 26 and 27.

As concerns the definition 'alkyl' in general, there is a contradiction between the Claims and the description. For the art skilled person the term 'alkyl' denotes a saturated, unsubstituted branched or unbranched aliphatic hydrocarbon chain, however, in the instant case the description defines this term in a much broader sense; see the 2nd paragraph on page 4.

The definition of the radicals R4 to R7 is too broad and in no way supported by the disclosure of the application as a whole. From the working examples and the limited number of activity data follows that the binding to the 5-HT receptors is apparently dependent on specific substituents, in the first line halogen.

It has to be assumed that the claims (in particular Claim 1 in its present wording) comprise a large number of speculative compounds which do not exhibit the alleged activities. The Applicant should ensure that the claims only cover compounds which actually solve the problem of providing compounds with a 5-HT₂ receptor binding affinity (Art.6, 33(3) PCT).

Finally the terms 'addition compounds' and 'prodrugs' at the end of claim 1 are unclear.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/00244

The method claim, Claim 31, is incomplete and therefore unclear in that it does not give any reaction conditions.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P020831W0	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB 00/ 00244	International filing date (day/month/year) 28/01/2000	(Earliest) Priority Date (day/month/year) 29/01/1999	
Applicant CEREBRUS PHARMACEUTICALS LIMITED et al.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PYRAZINO(AZA)INDOLE DERIVATIVES

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 00/ 00244

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20 to 30
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20 to 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

P B 00/00244

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/495 C07D471/14 C07D487/14 A61P25/00
A61P9/00 A61P1/00 //(C07D487/04,241:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 572 863 A (HOFFMANN-LA ROCHE) 8 December 1993 (1993-12-08) claims 1,14 -----	1,32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 May 2000

Date of mailing of the international search report

15/05/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P/B 00/00244

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 572863 A	08-12-1993	AU 662977 B	21-09-1995
		CA 2097465 A	06-12-1993
		CN 1080925 A	19-01-1994
		JP 6041132 A	15-02-1994
		NZ 247735 A	26-09-1995
		ZA 9303796 A	06-12-1993
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INTERNATIONAL SEARCH REPORT

International Application No.

PC 8 00/00244

A. CLASSIFICATION OF SUBJECT MATTER

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/495 C07D471/14 C07D487/14 A61P25/00
A61P9/00 A61P1/00 //(C07D487/04,241:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 572 863 A (HOFFMANN-LA ROCHE) 8 December 1993 (1993-12-08) claims 1,14 _____	1,32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

• **Special categories of cited documents :**

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

3 May 2000

Date of mailing of the international search report

15/05/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 00/00244

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20 to 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

P B 00/00244

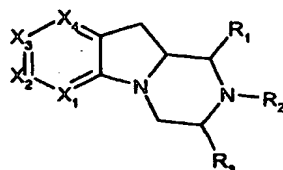
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 572863 A	08-12-1993	AU 662977 B	21-09-1995
		CA 2097465 A	06-12-1993
		CN 1080925 A	19-01-1994
		JP 6041132 A	15-02-1994
		NZ 247735 A	26-09-1995
		ZA 9303796 A	06-12-1993



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) -

(51) International Patent Classification ⁷ : C07D 487/04, A61K 31/495, C07D 471/14, 487/14, A61P 25/00, 9/00, 1/00 // (C07D 487/04, 241:00, 209:00)		A1	(11) International Publication Number: WO 00/44753 (43) International Publication Date: 3 August 2000 (03.08.00)
(21) International Application Number: PCT/GB00/00244 (22) International Filing Date: 28 January 2000 (28.01.00) (30) Priority Data: 9902047.1 29 January 1999 (29.01.99) GB (71) Applicant (for all designated States except US): VERNALIS RESEARCH LIMITED [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, David, Reginald [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). BENTLEY, Jon, Mark [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). DAVIDSON, James [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). DUNCTON, Matthew, Alexander, James [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB). PORTER, Richard, Hugh, Phillip [GB/GB]; Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA (GB).		(74) Agent: HOWARD, Paul, Nicholas; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: PIRAZINO(AZA)INDOLE DERIVATIVES



(I)

(57) Abstract

A chemical compound of formula (I) wherein: R₁ to R₃ are independently selected from hydrogen and lower alkyl; X₁ is selected from N and C-R₄; X₂ is selected from N and C-R₅; X₃ is selected from N and C-R₆; X₄ is selected from N and C-R₇; R₄, R₅ and R₇ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, alkoxy, aryloxy, alkoyl, aryloyl, arylthio, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino, nitro, cyano, carboalkoxy, carboaryloxy and carboxy; and R₆ is selected from hydrogen, halogen, alkyl, aryl, aryloxy, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, alkylamino, dialkylamino and cyano; with the proviso that R₄ to R₇ are not all selected as hydrogen, and pharmaceutically acceptable salts and addition compounds and prodrugs thereof; use thereof in therapy, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and especially for the treatment of therapy.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 00/ 00244

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20 to 30
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 20 to 30
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 00/00244

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 572863	A	08-12-1993	AU	662977 B	21-09-1995
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INTERNATIONAL SEARCH REPORT

Intern Application No

PCT/GB 00/00244

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/495 C07D471/14 C07D487/14 A61P25/00
 A61P9/00 A61P1/00 //(C07D487/04, 241:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 572 863 A (HOFFMANN-LA ROCHE) 8 December 1993 (1993-12-08) claims 1,14	1,32



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

3 May 2000

Date of mailing of the international search report

15/05/2000

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